SYNOPSIS:

"Synthesis and SAR Studies of New Benzothiazepine and Benzodiazepine Derivatives as Biologically Active Molecules"

Swami Ramanand Teerth Marathwada University

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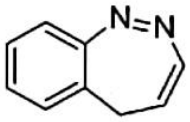
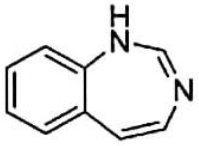
1. Introduction:

Benzodiazepines are nitrogen heterocycles having a six-membered benzene ring system fused to a seven-membered fused ring system with two nitrogen atoms[1]. Benzodiazepines are classified into six types of classes, which depend upon the position of the heteroatom Nitrogen in the ring. (Figure 2)



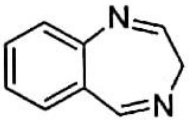
1,2-benzodiazepine

1



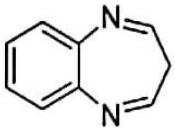
1,3-benzodiazepine

2



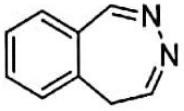
1,4-benzodiazepine

3



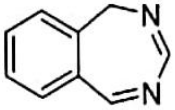
1,5-benzodiazepine

4



2,3-benzodiazepine

5

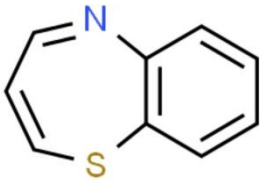


2,4-benzodiazepine

6

(Fig-2)

Benzothiazepines are a bicyclic heteroaromatic compound featuring a seven-membered ring containing nitrogen and sulfur, which is attached to a benzene structure[2]. (Figure.3).



Benzothiazepines

(Fig. 3)

2. The importance of the proposed research:

1. **Benzodiazepines** are a crucial class of compounds with diverse therapeutic and biological activities. They are widely used for their antianxiety, sedative, antidepressant, anticonvulsant, neuroleptic, and hypnotic properties. Additionally, benzodiazepine derivatives have shown efficacy as anti-inflammatory, antiviral, anti-HIV, antimicrobial, and antitumor agents. The benzodiazepine nucleus is also integral in various pharmacological applications, including antihypertensive, antiasthmatic, analgesic, cardiovascular modulation, vasodilation, platelet aggregation inhibition, antiulcer, antidementia, antibacterial, antifungal, and insecticidal activities. Key compounds within this class are used to treat conditions such as HIV infection, epilepsy, psychosis, angina pectoris, hypertension, and arrhythmias[3].

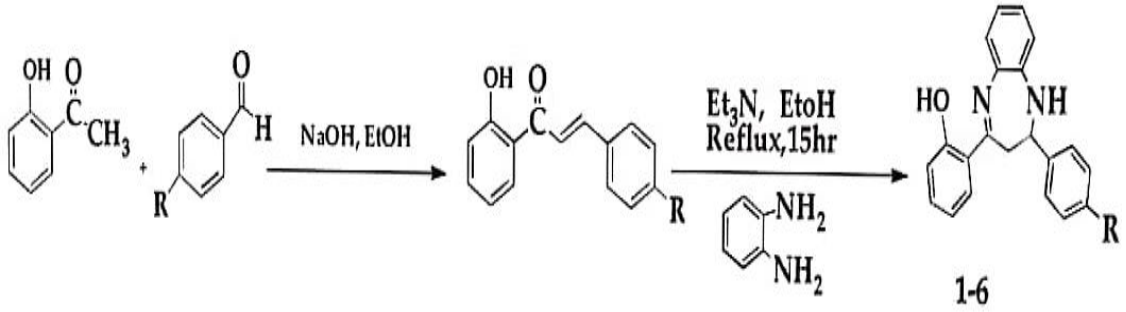
2. **Benzothiazepine** is a key heterocyclic structure with significant relevance in medicinal chemistry, as it is found in various bioactive compounds. It functions as a crucial "biolinker" in the synthesis of bioactive molecules and serves as an essential framework for developing new compounds. Benzothiazepine derivatives exhibit a wide range of pharmacological activities, including calcium channel blocking, central nervous system effects, anti-HIV properties, ACE inhibition, as well as antimicrobial, antifungal, and anticancer activities[4,5].

3. Objectives of the research:

1. Review of Previous Studies: Review the scientific literature related to Benzodiazepines and Benzothiazepines compounds.
2. Development and Application of New Synthesis Methods: Develop and apply new methods for synthesizing Benzodiazepines and Benzothiazepines compounds using different approaches.
3. Spectroscopic Analysis: Perform spectroscopic analysis of the resulting compounds using techniques such as IR spectroscopy and nuclear magnetic resonance (NMR) to determine their chemical structures.
4. Study of Pharmacological Activity: Investigate the pharmacological activity of the prepared compounds.

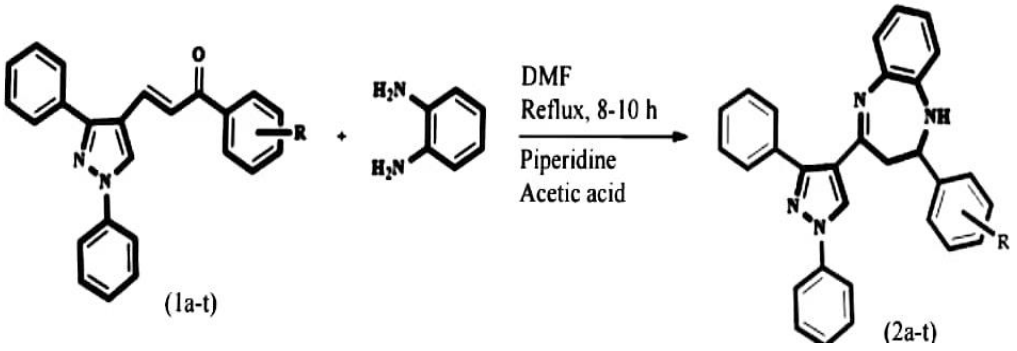
4. Literature review:

1. Haq, Faizan Ul, *et al*[6]. have explored new antidepressant agents by synthesizing and testing various benzodiazepine analogues in mice. After preparing these compounds and confirming their structures, the researchers assessed their antidepressant effects using forced swim and tail suspension tests. Significant reductions in immobility time indicated promising antidepressant activity for certain compounds. Additionally, these compounds enhanced GABA levels in the brain, suggesting a potential mechanism for their antidepressant effect.



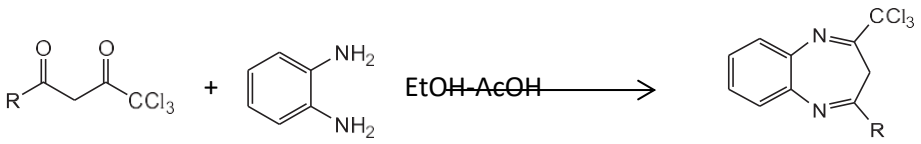
Scheme(1)

2. Desai, N. C., Joshi, S. B., & Khedkar, V. M[7], have presented a one-pot synthesis of pyrazole derivatives containing benzodiazepine moieties and evaluated their antimicrobial activities. The synthesized compounds were characterized using various spectral techniques. The antimicrobial testing revealed that some derivatives exhibited strong antibacterial and antifungal activities. Molecular docking studies provided insights into the binding interactions of these compounds with the microbial target DNA gyrase, helping to understand their potential as antimicrobial agents.



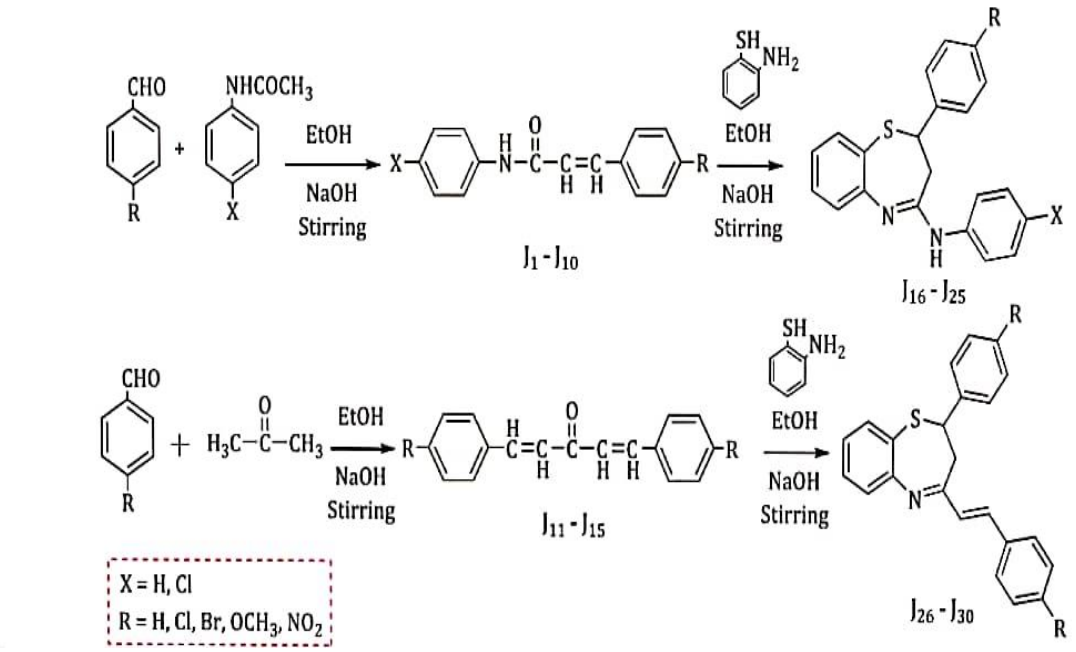
Scheme(2)

3. Myshkina, O.A. *et al*[8]. focused on synthesizing a series of 4-substituted 2-trichloromethyl-3H-1,5-benzodiazepines and evaluated their antimicrobial and antinociceptive properties. The compounds were synthesized through the reaction of specific β-diketones with o-phenylenediamine, optimized for yield. X-ray diffraction studies revealed structural details, including molecular packing and halogen bonding interactions. The synthesized benzodiazepines showed varying degrees of antimicrobial and antinociceptive activities, with some compounds demonstrating notable effectiveness in these areas. The study also assessed the acute toxicity of these compounds, confirming their low toxicity.



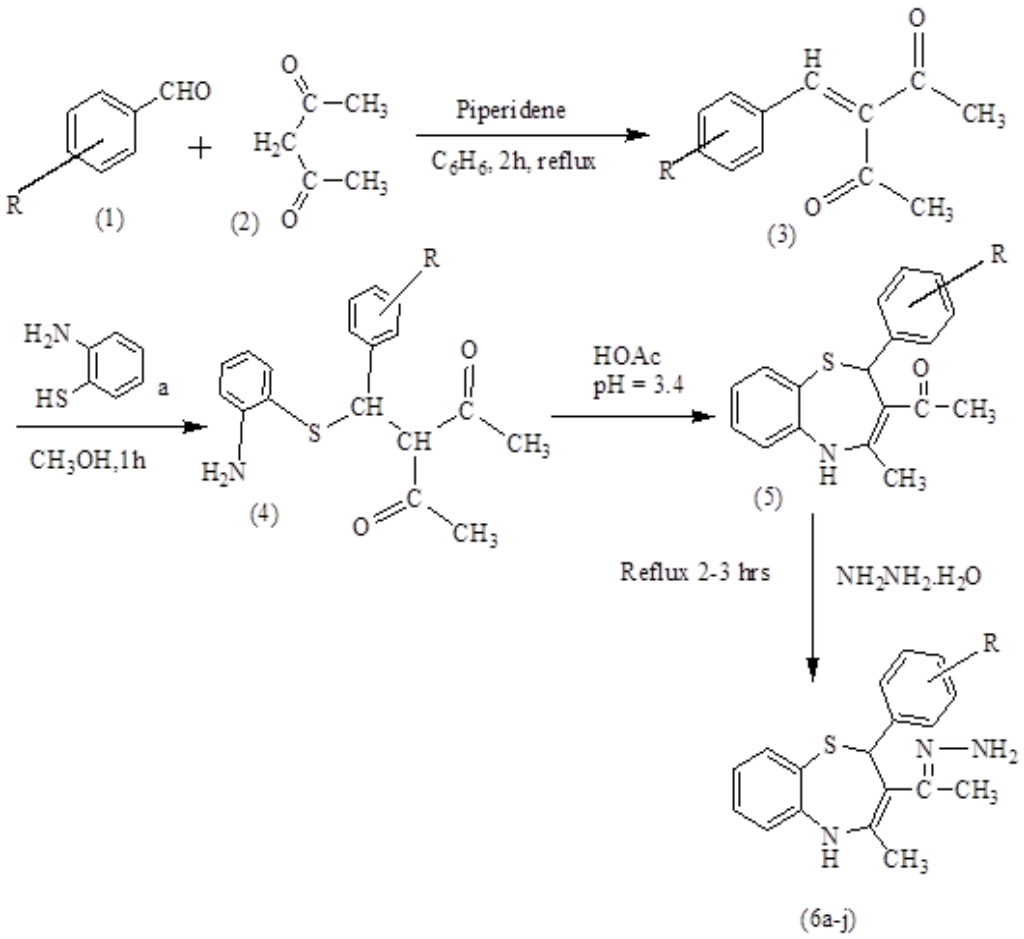
Scheme(3)

4. Jasim, Saad Salem, et al[9]. focused on synthesizing new 1,4-thiazepine compounds by reacting diphenyl acrylamides with diphenyl dienones in the presence of ortho-mercaptoaniline. The reaction takes place in an alkaline medium using ethanol as a solvent. The synthesized compounds were identified through various spectroscopy techniques, and their purity was confirmed by thin-layer chromatography. Their antibacterial activity was tested against several gram-positive and gram-negative bacteria, showing notable efficacy at higher concentrations. The study also explored the relationship between compound structure and antibacterial effectiveness, particularly highlighting the role of electron-withdrawing groups.



Scheme(4)

5. Chaudhri, V. K., Pathak, D., & Hussain, Z.[10]. focused on the synthesis of new substituted 1,5-benzothiazepine derivatives designed to retain anticonvulsant properties while minimizing toxicity. Various compounds were synthesized and characterized using chromatographic and analytical methods. Their anticonvulsant activity was evaluated using the maximal electroshock model, with the most effective derivative identified. Additionally, the safety of this compound was assessed through neurotoxicity and acute oral toxicity testing. The aim is to develop novel, less toxic anticonvulsant agents.



Scheme(5)

5. Proposed Research Methodology:

Studying the New synthetic methods or modifications in existing methodologies by using new reagents with emphasis on normalizing reaction conditions, increasing yields, and rapid reactions will be studied.

1. Any two synthetic schemes for Benzodiazepines.
2. Any two synthetic schemes for Benzothiazepines.

   From Chalcones

6. The characterization of the compounds will be carried out using spectroscopic techniques such as:

i. IR

ii. ^{1}H NMR

iii. ^{13}C NMR

iv. Mass spectrometry.

7. Expected Outcomes of Research Work Proposed:

1. Development of efficient synthesis routes for preparing new Benzodiazepines and Benzothiazepines derivatives.
2. Study of the biological and SAR effectiveness of proposed new chemical compounds.
3. Publication of results in scientific journals to contribute to the field of chemistry.

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Research Guide